AMENDMENTS TO THE SPECIFICATION

Please insert the following section heading at page 2, between lines 18 and 19 of the originally filed specification:

Summary of the Invention

Please insert the following section heading at page 3, between lines 15 and 16 of the originally filed specification:

Brief Description of the Invention

Figure 1 schematically depicts the spatial arrangement of the subsites of DHODH.

Figure 2 shows the minimal grid screen used for crystallization trails.

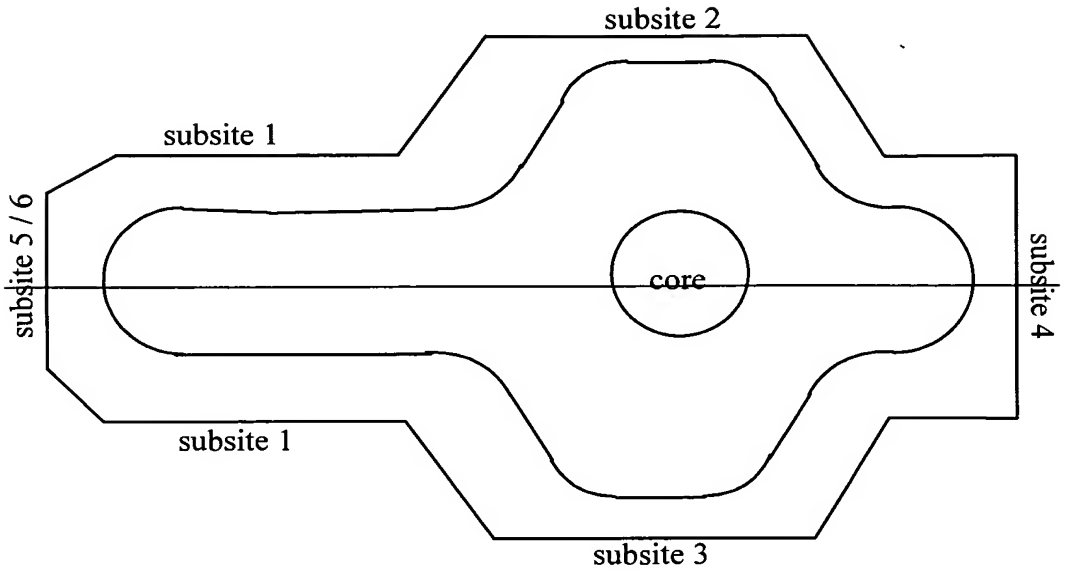
Detailed Description of the Invention

Please amend the paragraph beginning on page 9, line 1 of the originally filed specification as follows:

In the following a detailed description of identified subsites is provided. Residue numbering and atom labeling is identical to the numbering and labeling in ~~Fig. 2, 3 and 4~~ Tables 29, 30, and 31.

Please amend the paragraph beginning on page 16, line 1 of the originally filed specification as follows:

In ~~Fig.~~ Figure 1, the spatial arrangement of the subsites is depicted schematically.



~~Fig. 1~~

Please amend the paragraph beginning on page 16, line 12 of the originally filed specification as follows:

Analysis of the three dimensional structures of human DHODH in complex with ligands presented here clearly shows a new binding mode for inhibitors containing a carboxylic acid group. This binding mode differs from the brequinar-like binding mode in interacting not with subsite 2 but with subsite 3, termed the second anion binding site. In particular this is true for inhibitor compounds 1, 4, 5, 7 and 8 as can be seen from ~~figure 2~~ Table 29. This so far unobserved binding mode will be termed "non-brequinar-like" binding mode in the following.

Please amend the paragraph beginning on page 22, line 25 of the originally filed specification as follows:

In one embodiment, the atomic coordinates used in the method are the atomic coordinates set forth in ~~Figs. 2, 3 and 4~~ Tables 29, 30, and 31. It is to be understood that the coordinates set forth in ~~Figs. 2, 3 and 4~~ Tables 29, 30, and 31 can be transformed, for

example, into a different coordinate system, in ways known to those of skill in the art without substantially changing the three dimensional structure represented thereby.

Please amend the paragraph beginning on page 23, line 21 of the originally filed specification as follows:

The first method includes the steps of (1) identifying one or more functional groups capable of interacting with one or more subsites of the DHODH ubiquinone binding site; and (2) identifying a scaffold which presents the functional group or functional groups identified in step 1 in a suitable orientation for interacting with one or more subsites of the DHODH ubiquinone binding site. The compound which results from attachment of the identified functional groups or moieties to the identified scaffold is a potential inhibitor of DHODH. The DHODH ubiquinone binding site is, generally, defined by the atomic coordinates of a polypeptide comprising the DHODH ubiquinone binding site, for example, the atomic coordinates set forth in ~~Figs. 2, 3 and 4~~ Tables 29, 30, and 31.

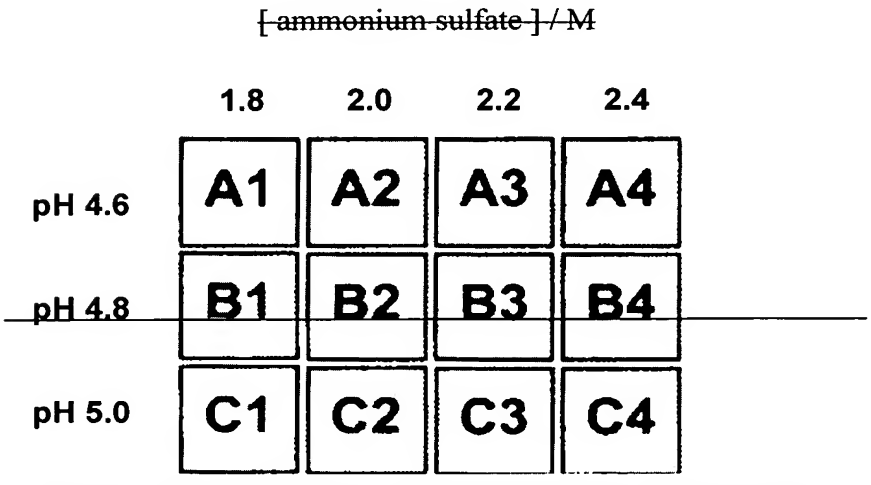
Please amend the paragraph beginning on page 23, line 30 of the originally filed specification as follows:

The second method comprises the steps of (1) identifying one or more functional groups or moieties capable of interacting in a similar way as one or more functional groups or moieties of the co-crystallized ligand, and (2) identifying a scaffold which presents the functional group or functional groups identified in step 1 in a suitable orientation for interacting in a similar way as one or more functional groups or moieties of the co-crystallized ligand. The compound which results from attachment of the identified functional groups or moieties to the identified scaffold is a potential inhibitor of DHODH. The co-crystallized ligand is, generally, defined by the atomic coordinates of a ligand complexed in

the polypeptide comprising the DHODH ubiquinone binding site, for example, the atomic coordinates set forth in ~~Figs. 2, 3 and 4~~ Tables 29, 30, and 31.

Please amend the paragraph beginning on page 32, line 25 of the originally filed specification as follows:

Human his10-hDHODH(Met30-Arg396) was co-crystallized with compound 1 and compound 2 at 20°C using the hanging-drop vapour diffusion method. Drops were formed by mixing equal amounts of 20 mg/ml protein in 50 mM HEPES pH 7.7, 400 mM NaCl, 30% glycerol, 1 mM EDTA and 10 mM N,N-dimethylundecylamin-N-oxide (C11DAO) with a precipitant solution of 0.1 M acetate pH 4.6 – 5.0, 40 mM C11DAO, 20.8 mM N,N-dimethyldecylamine-N-oxide (DDAO), 2 mM dihydroorotate (DHO), 1.8 – 2.4 M ammonium sulfate, 1 mM compound 1 or 2. The hanging drops were incubated against 0.5 mL reservoir of 0.1 M acetate pH 4.8, 2.4 – 2.6 M ammonium sulfate and 30% glycerol. The crystallization conditions were screened by variation of pH versus ammonium sulfate concentration using a small grid screen (see ~~figure 5~~ figure 2):



~~Figure 5: Minimal grid screen used for crystallization trails.~~

Please amend the paragraph beginning on page 40, line 23 of the originally filed specification as follows:

A pdb file for compound 1 was created using the program MOE (Chemical Computing Group Inc., MOE 2002.02). After energy minimization the compound was built into the electron density manually. Topology and parameter files for compound 1 were created using the program Xplo2d (Uppsala Software Factory; Kleywegt, G.M.(1997) J. Mol. Biol. 273, 371-376). After an additional round of model building and water picking using CNX another complete round of refinement was performed. The final model included the DHODH(Met30-Arg396) protein, the cofactor flavinmononucleotide (FMN), one orotate molecule (ORO), one acetate molecule (ACT), two sulfate ions (SO4), one molecule of compound 1 (INH) and 153 water molecules (TIP) (see ~~figure 2~~ Table 29). The model is well refined and has very good geometry. The refinement process which included data from 12.0 – 2.35 Å resulted in an R-factor of 18.5 % and a free R-factor of 21.7%. With the exception of glycine residues, 92.4 % (278) of the residues are located in the most favoured region of the ramachandran plot and 7.6 % (22) cluster in the additional allowed regions. Table 13 summarizes the refinement statistics for the inhibitor compound 1 in complex with human DHODH. Values in parentheses give the R-factor and R_{free}-factors, respectively, for the last resolution bin ranging from 2.50 to 2.35.

Please amend the paragraph beginning on page 42, line 17 of the originally filed specification as follows:

Pdb files for the compound 2 in conformation A and B were created using the program MOE (Chemical Computing Group Inc., MOE 2002.02) . Both compounds were energy minimized and built into the electron density manually. Topology and parameter files for compound 2 were created using the program Xplo2d (Uppsala Software Factory;

Kleywegt, G.M.(1997) J. Mol. Biol., 273, 371-376). After an additional round of model building and water picking using CNX, another complete round of refinement was performed. The final model included the human DHODH(Met30-Arg396) protein, the cofactor flavinmononucleotide (FMN), one orotate molecule (ORO), one acetate molecule (ACT), four sulfate ions (SO4), one molecule of compound 2 (INH) either in conformation A or conformation B and 250 water molecules (TIP) (see ~~figures 3 and 4~~ Tables 30 and 31). The models are well refined and show very good geometry. The refinement process which included data from 12.0 – 2.4 Å resulted in an R-factor of 17.5 % and a free R-factor of 21.1% for conformation A complex and an R-factor of 17.6 % and a free R-factor of 21.6% for conformation B complex, respectively. With the exception of glycine residues, 91.7 % (276) of the residues are located in the most favoured region of the ramachandran plot and 8.3 % (24) cluster in the additional allowed regions.. Table 14 summarizes the refinement statistics for compound 2 in complex with human DHODH. Values in parentheses give the R-factor and R_{free}-factors, respectively, for the last resolution bin ranging from 2.55 to 2.40.

Please amend the paragraph beginning on page 82, line 11 of the originally filed specification as follows:

~~Figure 2~~ Table 29

Please amend the paragraph beginning on page 168, line 1 of the originally filed specification as follows:

~~Figure 3~~ Table 30

Please amend the paragraph beginning on page 253, line 1 of the originally filed specification as follows:

~~Figure 4~~ Table 31

Page 353 of the clean copy of the attached substitute specification (Abstract), after the last line, beginning on a new page, please insert the attached Sequence Listing.